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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,143	EINAT ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3-5,8-10 and 12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,11,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/4/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The Election filed 10/06/06 in response to the Office Action of 04/03/06 is acknowledged and has been entered.

Applicants' election with traverse of Group II, claims 1-11 and the IDH inhibitor species of siRNA is acknowledged.

Applicants argue for the withdrawal of the restriction requirement in view of the election of Group II, claims 1-11, and the addition of claims 25 and 26. Applicants argue that the invention of Group II is drawn to a method for treatment of an apoptosis related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide. Applicants argue that claims 25 and 26 are drawn to a species for treatment of an apoptosis related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide which is an siRNA. Applicants argue that the claims of elected Group II are not independent from the claims of added claims 25 and 26. Applicants argue that there would not be a serious burden on the Examiner if restriction is not required between the claims of Group II and added claims 25 and 26. Applicants argue that therefore that claims 1-11 and 25 and 26 should be examined on the merits.

Applicants' arguments have been considered and have been found to be persuasive; claims 25 and 26 will be examined with Group II as drawn to the species siRNA.

The issues remain the same and the restriction requirement is deemed to be proper and is therefore made FINAL.

2. Claims 1-25 are pending.

3. Claims 3-5, 8-10, and 12-24 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1, 2, 6, 7, 11, 25 and 26 as drawn to siRNA as the IDH inhibitor are currently under consideration.

Specification

5. The amendment filed 11/03/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The new SEQ ID NO: 6 in Figure 4.

Applicant is required to cancel the new matter in the reply to this Office Action.

6. The specification is objected to on page 39, line 15, for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicants must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). *Failure to supply the appropriate sequences identification numbers in response to this action will be considered non-responsive.*

7. The disclosure is objected to because of the following informalities: The word polynucleotide in the heading on page 54 is missing an "o".

Appropriate correction is required.

Drawings

8. The drawings are objected to because the specification does not define what IRT_4C1 in Figure 8 is. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

9. Claims 1, 2, 6, 7, 11, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to a method for treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide, in a dosage sufficient to inhibit IDH so as to thereby treat the subject and a method for potentiating a chemotherapeutic treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the human IDH polypeptide in conjunction with a chemotherapeutic agent, wherein the IDH inhibitor is an siRNA for the IDH gene.

The specification teaches that an "apoptosis-related disease" is a disease whose etiology is related either wholly or partially to the process of apoptosis. The disease may be caused either by a malfunction of the apoptotic process (such as in cancer or an autoimmune disease) or by over activity of the apoptotic process (such as in certain neurodegenerative diseases), see p.3 lines 14-18.

The specification teaches that HeLa cells, a cervical cancer cell line, transiently transfected with an IDH siRNA (5'AATCGTGATGCCACCAACGAC'3) were sensitized to doxorubicin mediated apoptosis, see p. 39, lines 14-21 and Fig. 10.

The teachings of the specification cannot be extrapolated to the enablement of the claims because 1) no nexus has been established between inhibition of the IDH polypeptide and any apoptosis-related disease because the artifacutal nature of cultured cells is well known in the art and the unpredictability of drug development for apoptosis-related diseases such as cancer is also well known in the art and 2) no nexus has been established between the treatment of the cells with siRNA for the IDH gene and an effect on any IDH polypeptide and those of skill in the art are aware that non-specific, off-target effects occur when using siRNA to inhibit mRNA and the unpredictability of polynucleotide based therapies for apoptosis-related diseases such as cancer is also well known in the art.

1) In particular, as drawn to the artifactual nature of cultured cells, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the

cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Thus, based on the cell culture data presented in the specification, in the absence of data provided from primary tumor cells, no one of skill in the art would believe it more likely than not that the claimed

invention would function as claimed, that is as a method for treatment of an apoptosis-related disease or for potentiating a chemotherapeutic treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide, in a dosage sufficient to inhibit IDH so as to thereby treat the subject, wherein the IDH inhibitor is an siRNA for the IDH gene, based only on the cell culture data provided.

Furthermore it is well known that the art of anti-cancer, an apoptosis-related disease, drug development is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042 teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed method for treatment of an apoptosis-related disease or for potentiating a chemotherapeutic treatment of an apoptosis-related disease by inhibiting an IDH polypeptide with an siRNA would be effective based only on the cell culture data provided.

2) Furthermore, as drawn to the ability of the siRNA to inhibit any IDH polypeptide, the specification does not teach that any IDH polypeptide was inhibited at any level by the siRNA disclosed in the specification and the specification does not teach that the siRNA used was specific for IDH. Although in vitro effects of the transfected siRNA were seen on the sensitivity

of cell line to doxorubicin induced apoptosis (p. 39, example 2b), those of skill in the art are aware that non-specific, off-target effects occur when using siRNA. In particular, Pei and Tuschl (Nature Methods, 2006, 3: 670-676) teach that siRNAs may nonspecifically target unrelated genes with only partial sequence-complementarity, see Abstract and p. 670, left column. Pei and Tuschl teach that it is important to experimentally control off-target effects or to dilute the off-target effects beyond the detection limit by co-delivering several different target-specific siRNAs, see p. 674, left column. Thus, in the absence of additional evidence that the siRNA used 1) inhibited the intended target and 2) did not have non-specific, off-target effects that contributed to the observed phenotype, one of skill in the art could not reasonably predict whether or not the observed effects of the siRNA to IDH on apoptosis were the result of specific inhibition of IDH or other off-target effects of the siRNA used. Thus, based on those studies, it cannot be predicted from the information in the specification that the IDH polypeptide was specifically inhibited by the siRNA used and that this inhibition positively correlated with an effect on apoptosis.

Furthermore, it is well known in the art, based on experience with antisense RNA molecules, that nucleic acid based therapies like siRNA are unpredictable for apoptosis related diseases like cancer.

In particular, Gura (Science, 1995, 270:575-577) teaches that researchers have many concerns with the antisense therapy. Gura discloses, "The biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular

problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue in vitro (page 576, col 3, para 1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model. Although drawn to antisense molecules, one of skill in the art would expect that siRNA molecules would also be subject to similar unpredictable behavior since types of treatment rely on the introduction of short, sequence specific nucleic acid molecules that target mRNA to a patient for treatment

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as

contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. If applicant were able to overcome the rejections set forth above, claims 1, 2, 6, 7, 11, 25 and 26 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of an apoptosis-related disease or for potentiating a chemotherapeutic treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide, **wherein the IDH polypeptide is SEQ ID NO: 2 or 4**, in a dosage sufficient to inhibit IDH so as to thereby treat the subject, wherein the IDH inhibitor is an siRNA for the IDH gene, **wherein the IDH gene is SEQ ID NO: 1 or 3;** does not reasonably provide enablement for a method for treatment of an apoptosis-related disease or for potentiating a chemotherapeutic treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the **IDH polypeptide**, in a dosage sufficient to inhibit IDH so as to thereby treat the subject, wherein the IDH inhibitor is an siRNA for the IDH

gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide, in a dosage sufficient to inhibit IDH so as to thereby treat the subject and a method for potentiating a chemotherapeutic treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the human IDH polypeptide in conjunction with a chemotherapeutic agent, wherein the IDH inhibitor is an siRNA for the IDH gene.

This means that inhibition of **any** IDH polypeptide will be effective for treatment of an apoptosis related disease or for potentiating a chemotherapeutic treatment of an apoptosis-related disease and that the siRNA for the IDH gene taught in the specification (SEQ ID NO: 6) will inhibit **any** IDH polypeptide.

The specification teaches that "IDH polypeptide" refers to the polypeptide of the IDH1 or IDH2 gene derived from any organism, optionally man, splice variants and fragments thereof retaining viability activity, and homologs thereof, preferably having at least 70%, more preferably at least 80%, even more preferably at least 90% or 95% homology thereto. The specification teaches that, in addition, this term is understood to encompass polypeptides resulting from minor alterations in the IDH1 or IDH2 coding sequence, such as, inter alia, point mutations, substitutions deletions and insertions which may cause a difference in a few amino acids between the resultant polypeptide and the naturally occurring IDH1 or IDH2. The specification teaches that polypeptides encoded by nucleic acid sequences which bind to the

IDH1 or IDH2 coding sequence or genomic sequence under conditions of highly stringent hybridization, which are well-known in the art, are also encompassed by this term. The specification teaches that he polypeptide sequence of IDH1 is depicted in FIG. 1 (SEQ ID NO: 2). The polypeptide sequence of IDH2 is depicted in FIG. 2 (SEQ ID NO: 4), see para bridging p. 6 and 7.

Thus, the claims read on an IDH polypeptide wherein the IDH polypeptide comprises 7 amino acids because 7 amino acids is the smallest whole integer of a polypeptide having at least 70% identity of a given number of amino acids, i.e. 70% of 10 amino acids = 7 amino acids.

One cannot extrapolate the teachings of the specification to the scope of the claims in view of the teachings of the specification that an IDH polypeptide includes can include sequences with numerous types of amino acid sequence changes, because 1) there are no teachings that the variant polypeptides will function in the method claimed, i.e. as an IDH polypeptide that when inhibited will allow for treatment of an apoptosis-related disease and one could not predictably identify which molecules would act as inhibitors of these broadly claimed IDH polypeptides 2) the claims as broadly written are drawn to splice variants of IDH and one of ordinary skill in the art could not predictably identify which molecules would act as inhibitors of these broadly claimed IDH polypeptides 3) the single siRNA for IDH taught in the specification would not be expected to inhibit the scope of IDH polypeptides contemplated because it is well known in the art that siRNAs are sequence specific inhibitors of mRNA and the single siRNA taught in the specification (SEQ ID NO: 6) would not be predicted to inhibit the numerous IDH mRNAs for the numerous variants of IDH polypeptide contemplated.

1) As drawn to the variant polypeptides, a polypeptide sequence with only 70% identity to IDH (~7 amino acids) or a larger IDH polypeptide with numerous undefined amino acid variations cannot reasonably be predicted to function as a regulator of an apoptosis-related disease as required by the method as claimed and one could not predictably identify which molecules would act as inhibitors of these broadly claimed IDH polypeptides.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47

with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In view of the unlimited and undefined alterations in the IDH polypeptides contemplated in the specification and claimed, the function of an altered IDH polypeptide would not be expected to be the same as that of the unaltered IDH polypeptide and the effects of modulating the claimed protein could not be extrapolated to effects on IDH with a reasonable expectation of success. Furthermore one could not predictably identify which molecules that would act as inhibitors of these broadly claimed IDH polypeptides with a reasonable expectation of success.

Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al, the effects of unlimited and undefined changes in an IDH polypeptide on its activity, and by extension, the inhibitors of that activity, could not be predicted. Thus it would require undue experimentation for one of ordinary skill in the art to practice the method as claimed.

2) As drawn to splice variants, it is well known in the art that splice variants are mRNA molecules composed of differing mRNA sequences. In particular, Darnell et al. (Molecular Biology of the Cell, 1990, p. 434-435) teach that the rat troponin T gene can give rise to 64 possible mRNA sequences and that the α-Tropomyosin gene can also give rise to several different transcripts, see Fig. 11-42 and p. 434, right column.

These references serve to demonstrate that one of skill in the art could not predictably identify which molecules that would act as inhibitors of these broadly claimed IDH polypeptides,

inclusive of splice variants, with a reasonable expectation of success. Thus, undue experimentation would be required to make and use the invention as broadly claimed.

3) As drawn to the ability of SEQ ID NO: 6 siRNA to inhibit the numerous contemplated IDH polypeptides, it is well known in the art that siRNA are sequence specific inhibitors of mRNA that the activity of any given siRNA requires experimental validation due to the sensitivity of siRNAs to the nucleotide composition of the targeted sequence for effective functioning.

In particular, Pei and Tuschl teach that, siRNAs are generally designed to be fully complementary to its target mRNA and are of 21-23 nucleotides in length, see Box 1. Pei and Tuschl teach that small positional shifts along the target mRNA alter siRNA function in an apparently unpredictable manner, see p.670, left column. Pei and Tuschl teach that although computation tools have been developed to effectively select siRNAs, they do not yet alleviate the need for experimental validation.

Thus, given the above, one of ordinary skill in the art would not reasonably predict that the single siRNA taught in the specification would inhibit all IDH mRNAs encoding the various contemplated IDH polypeptides given the expected differences in mRNA primary and secondary structure. Although Applicants may argue that siRNA to the mRNAs encoding the variant IDH polypeptides could be designed with computational tools, the computational tools do not reliably predict functional siRNAs without additional experimentation. Thus, undue experimentation would be required to practice the method as broadly claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the

art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as broadly claimed with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

11. Claims 1, 2, 6, 7, 11, 25 and 26 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1, 2, 6, 7, 11, 25 and 26 are drawn to a method for treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the IDH polypeptide, in a dosage sufficient to inhibit IDH so as to

thereby treat the subject and a method for potentiating a chemotherapeutic treatment of an apoptosis-related disease in a subject comprising administering to said subject a therapeutically effective amount of an inhibitor of the human IDH polypeptide in conjunction with a chemotherapeutic agent, wherein the IDH inhibitor is an siRNA for the IDH gene. It is noted that the specification teaches that "IDH polypeptide" refers to the polypeptide of the IDH1 or IDH2 gene derived from any organism, optionally man, splice variants and fragments thereof retaining viability activity, and homologs thereof, preferably having at least 70%, more preferably at least 80%, even more preferably at least 90% or 95% homology thereto. The specification teaches that, in addition, this term is understood to encompass polypeptides resulting from minor alterations in the IDH1 or IDH2 coding sequence, such as, inter alia, point mutations, substitutions deletions and insertions which may cause a difference in a few amino acids between the resultant polypeptide and the naturally occurring IDH1 or IDH2. The specification teaches that polypeptides encoded by nucleic acid sequences which bind to the IDH1 or IDH2 coding sequence or genomic sequence under conditions of highly stringent hybridization, which are well-known in the art, are also encompassed by this term, see p. 6 lines 14-31.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical

species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with

a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the broadly claimed IDH polypeptide to be inhibited for treatment of an apoptosis-related disease, per Lilly by structurally describing a representative number of such IDH polypeptides or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the broadly claimed IDH polypeptides to be inhibited for treatment of an apoptosis-related disease in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any of the broadly claimed IDH polypeptides to be inhibited for treatment of an apoptosis-related disease, nor does the specification provide any partial structure of such IDH polypeptides, nor any physical or chemical characteristics of the IDH polypeptides nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the

specification discloses, SEQ ID NOs: 2 and 4, this does not provide a description of the broadly claimed IDH polypeptide to be inhibited for treatment of an apoptosis-related disease that would satisfy the standard set out in Enzo.

The specification also fails to describe the broadly claimed IDH polypeptides to be inhibited for treatment of an apoptosis-related disease by the test set out in Lilly. The specification describes only two IDH polypeptides. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the broadly claimed IDH polypeptide to be inhibited for treatment of an apoptosis-related disease that is required to practice the claimed invention. Since the specification fails to adequately describe the broadly claimed IDH polypeptides to be inhibited for treatment of an apoptosis-related disease, it also fails to adequately describe the method for treatment of an apoptosis-related disease by inhibiting the broadly claimed IDH polypeptides.

12. Claims 25 and 26 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 25 and 26 are drawn to the method according to claim 1 or claim 7, wherein the inhibitor is an siRNA for the IDH gene. It is noted that the specification teaches that "IDH gene"- the isocitrate dehydrogenase 1 coding sequence open reading frame, as shown in FIG. 1 (SEQ ID NO:1), or the isocitrate dehydrogenase 2 coding sequence open reading frame, as shown in FIG.

2 (SEQ ID NO:3), or any homologous sequence thereof preferably having at least 70% identity, more preferable 80% identity, even more preferably 90% or 95% identity. This encompasses any sequences derived from SEQ ID NO: 1 or SEQ ID NO:3 which have undergone mutations as described herein, see p. 6 lines 6-12.

As it is drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an siRNA for the IDH gene, per Lilly by structurally describing a representative number of such IDH siRNAs or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification

can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the broadly claimed siRNA for the IDH gene in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any of the broadly claimed siRNA for the IDH gene, nor does the specification provide any partial structure of such IDH siRNAs, nor any physical or chemical characteristics of the IDH siRNAs nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses, SEQ ID NOs: 6, this does not provide a description of the broadly claimed IDH polypeptide to be inhibited for treatment of an apoptosis-related disease that would satisfy the standard set out in Enzo.

The specification also fails to describe the broadly claimed siRNA for the IDH gene by the test set out in Lilly. The specification describes only one IDH siRNA. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the broadly claimed siRNA for the IDH gene that is required to practice the claimed invention. Since the specification fails to adequately describe the broadly claimed siRNA for the IDH gene, it also fails to adequately describe the method for treatment of an apoptosis-related disease with the broadly claimed siRNA for the IDH.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0890. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR

Notice to Comply	Application No. 10/618,143	Applicant(s) Einat et al.	
	Examiner Peter J. Reddig	Art Unit 1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The disclosure is lacking numerous sequence identifiers and sequence ID numbers, see the section titled "Sequence Listing" in the accompanying First Office Action on the Merits.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
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APPLICATION NO. /CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10/618,143	07/11/2003	Paz Einat	2094/6773-A/JPW/FHB

EXAMINER	
Peter Reddig, Ph.D.	
ART UNIT	**PAPER**
1642	

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must provide the appropriate SEQ ID NO: for the sequence on page 39, line 15.

If a complete reply has not been submitted by the time period set in the accompanying Office action (paper No 20061129) has expired, this application will become abandoned under 37 CFR 1.821(g).

Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (http://ww.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual-ePAVE)

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3.Hand Carry, Federal Express, United Parcel Service or other delivery service to:

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Reddig whose telephone number is 571-272-9031. The examiner can normally be reached on M-F 8:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foleycan be reached on 571-272-0890.

Peter Reddig, Ph.D.
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Sequence Count Sheet	Application/Control No.	Applicant(s)	
	10/618,143	Einat et al.	
	Examiner	Art Unit	
	Peter Reddig	1642	

DATE OF COUNT

Mark only one space below

☐ **(CRFN)** (CRF is unreadable; use CRF Diskette Problem Report)

☒ **(CRFD)** (CRF does not comply; use Notice to Comply)

☐ **(CRFR)** (CRF required but none submitted; use Notice to Comply)

☐ **(bona fide)** (second or subsequent letter to applicant reporting bona fide attempt to comply; use Notice to Comply and send copy of RSL)

☐ **(non bona fide)** (second or subsequent letter to applicant reporting non-bona fide attempt to comply; use Notice to Comply and send copy of RSL)